REMARKS

Claim 35 has been amended. Claims 1, 18-23, 30, and 35 are pending in the instant application. No new matter has been added as a result of the above-described amendments. The rejections set forth in the Office Action have been overcome by amendment or are traversed by argument below.

1. Rejection of claims 1, 18-23, 30, and 35 under 35 U.S.C. § 112, first paragraph

a. Rejection of claims 1, 18-23, 30, and 35 under the written description requirement of 35 U.S.C. § 112, first paragraph

The Office Action asserts a rejection of claims 1, 18-23, 30, and 35 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Action states that the specification does not provide an adequate written description of the claimed genus of trimeric polypeptides because it lacks a sufficient recitation of distinguishing identifying characteristics of the claimed genus. In particular, the Action states that while the only distinguishing identifying characteristic of the claimed genus is the ability of the recited trimeric polypeptides to induce proliferation or development of lymphocytes, the claims do not require that the recited trimeric polypeptides possess any particular conserved structure in order to maintain the desired biological activity.

With respect to claim 1, the Action states that absent a description of the common attributes or characteristics that identify members of the claimed genus, the recitation of the claimed polypeptide alone is insufficient to describe such a highly variant genus. The Action also states that the monomers set forth in SEQ ID NOs: 106, 107, and 108 do not constitute a representative number of species to describe the genus of claim 1.

With respect to claims 18 and 19, the Action states that while the tetranectin trimerising domain of SEQ ID NO: 81 has been adequately described, a trimeric polypeptide having a trimerising domain comprising a sequence having at least 68% (claim 18) or 92% (claim 19) amino acid sequence identity with the sequence of SEQ ID NO: 81 is not adequately described, because a

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skilled artisan cannot envision the structure of the trimeric polypeptides of the claimed genus. The Action also states that neither the specification nor the claims provide any guidance as to what changes can be made to the claimed trimeric polypeptides. The Action concludes that only the trimeric polypeptide monomers set forth in SEQ ID NOs: 106, 107, and 108, each of which comprises a cytokine binding domain and the tetranectin trimerising domain of SEQ ID NO: 81, satisfy the requirements of the written description requirement of 35 U.S.C. § 112, first paragraph.

Applicants respectfully disagree with the Action's assertion that the specification does not provide an adequate written description of the trimeric polypeptides of claim 1. To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention (*see* M.P.E.P. § 2163). An inventor can show possession by describing an actual reduction to practice of the claimed invention, by a clear depiction of the invention in detailed drawings or in structural chemical formulas, or by any description of sufficient, relevant, identifying characteristics (*i.e.*, structure or other physical and/or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of such identifying characteristics) (*id.*).

Applicants note that claim 1 recites a trimeric polypeptide comprising three monomers, each of said monomers comprising a specific binding member capable of binding a trimeric cytokine, and each of said monomers comprising a trimerising domain that is derived from tetranectin. With respect to the portion of the claimed trimeric polypeptide that is a specific binding member capable of binding a trimeric cytokine, the specification defines a specific binding member as "a member of a pair of molecules which have binding specificity for one another" (¶ 27 of specification), and defines trimeric cytokines as being "small proteins and fragments thereof, which are produced and secreted by a cell, and which elicit a specific response in a cell which has a receptor for that cytokine, e.g. by affecting the growth, division and/or function of the cell" (¶ 24).

The specification also lists a number of examples of trimeric cytokines, including macrophage migration inhibitory factor (MIF) and cytokines within the tumor necrosis factor ligand super family (TNFLSF) (¶ 25), which includes at least seventeen recognized ligands (*i.e.*, lymphotoxin alpha (LTA), tumor necrosis factor (TNF), lymphotoxin beta (LTB), OX-40L, CD40L, FasL, CD27L, CD30L, 4-1BB-L, TRAIL, RANKL, TWEAK, APRIL, BAFF, LIGHT, VEGI, and

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GITRL; ¶ 5; *see also* Table 1 on p. 3 of specification) that share a conserved trimeric C-terminal domain known as the "TNF homology domain" (THD) (¶ 25). In addition, the specification lists a number of examples of specific binding members that are capable of binding a trimeric cytokine, including receptors within the tumor necrosis factor superfamily (*e.g.*, TNFRSF1A, TNFRSF1B, LTBR, TNFRSF4, TNFRSF5, TNFRSF6, TNFRSF6B, TNFRSF7, TNFRSF8, TNFRSF9, TNFRSF10A, TNFRSF10B, TNFRSF10C, TNFRSF10D, TNFRSF11A, TNFRSF11 B, TNFRSF12, TNFRSF12L, TNFRSF13B, TNFRSF13C, TNFRSF14, NGFR, TNFRSF17, TNFRSF18, TNFRSF19, TNFRSF19L, TNFRSF21, TNFRSF22, and TNFRSF23; ¶ 31; *see also* Table 2 on p. 4); antibodies or antibody fragments that specifically bind trimeric cytokines (¶ 34); and antibody analogues or artificial antibodies (*e.g.*, proteins having the scaffold structure of C-type lectin-like domains (CTLD) such as the human tetranectin-based CTLD antibody analogues disclosed in the specification that are capable of binding TNF; ¶ 38). Applicants contend, therefore, that in view of the disclosure in the specification, one of ordinary skill in the art would readily recognize the types of molecules that are encompassed by the phrase "specific binding member capable of binding a trimeric cytokine."

With respect to the portion of the claimed trimeric polypeptide that is a trimerising domain that is derived from tetranectin, the specification states that such domains comprise a tetranectin trimerising structural element (also called TTSE), which is described in detail in International Publication No. WO 98/56906 (the '906 publication; *i.e.*, the PCT equivalent of U.S. Application No. 11/452,434, which is discussed below in section 3). The '906 publication teaches that the human tetranectin TTSE is 36 amino acids in length (*see* Exhibit A, which shows the amino acid sequence of the full-length, mature human tetranectin monomer, and in which the human tetranectin TTSE sequence is underlined). The amino acid residues that constitute the TTSE consensus sequence are indicated by bold uppercase letters. Finally, the amino acid residues of the TTSE sequence that constitute a portion of the repeated heptad are indicated by the lowercase letters a, b, c, d, e, f, or g. Of the 36 amino acid residues that form the TTSE, fifteen are conserved in human and murine tetranectin, the C-type lectin of bovine cartilage, and the C-type lectin of shark cartilage. The conserved residues are found at positions 26, 33, 36, 37, 40-42, and 44-51 of the full-length, mature human tetranectin sequence.

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While the '906 publication teaches that the residues at positions 26, 33, 36, 37, 40-42, and 44-51 constitute the TTSE consensus sequence, the '906 publication also teaches that a number of these residues can be substituted with other amino acid residues. For example, the '906 publication teaches that the cysteine residue at position 50 "should be mutagenized to serine, threonine, methionine or to any other amino acid residue in order to avoid formation of an unwanted inter-chain disulphide bridge, uncontrolled multimerisation, aggregation and precipitation of a polypeptide product harbouring this sequence" (*see* page 16, lines 9-16 of '906 publication; the instant application provides a similar disclosure in ¶41). The '906 publication also teaches that "one advantageous embodiment of the monomer polypeptide construct of the invention is one where at least one amino acid residue selected from the group consisting of amino acid residue nos. 6, 21, 22, 24, 25, 27, 28, 31, 32, 35, 39, 41, 42, is/are substituted by any non-helix breaking amino acid residue," and further discloses that "[a]ll these residues have been shown ***not*** to be directly involved in the intermolecular interactions which stabilize[] the trimeric complex between three TTSEs of native tetranectin monomers and it is therefore expected that these amino acids may be safely substituted with any amino acid which will not have an adverse effect on helix formation" (*see* page 21, lines 21-33; emphasis added). In addition, the '906 publication teaches that it is "preferred that the TTSE comprises a repeated heptad having the formula a-b-c-d-e-f-g (N to C), wherein residues a and d [*i.e.*, positions 26, 33, 37, 40, 44, 47, and 51] generally are hydrophobic amino acids" (*see* page 22, lines 7-10). Furthermore, while the '906 publication teaches that the "a" and "d" residues of the third heptad repeat (*i.e.*, the residues at positions 44 and 47 of the amino acid sequence shown in Exhibit A) in human and murine tetranectin, the C-type lectin of bovine cartilage, and the C-type lectin of shark cartilage are glutamine, the residues at these positions are only the "most preferred" residues (*see* page 22, lines 10-15).

Applicants note that a TTSE sequence that shares 68% identity with the consensus sequence shown in Figure 2 of the '906 publication would retain eleven of the fifteen residues of the consensus sequence. Similarly, a TTSE sequence that shares 75% identity would retain twelve residues, a TTSE sequence that shares 81% identity would retain thirteen residues, and a TTSE sequence that shares 87% or 92% identity would retain fourteen residues of the consensus sequence. In view of the express teachings in the '906 publication, which was published on December 17, 1998 (almost five years earlier than the filing date of the instant application), Applicants contend that one of

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ordinary skill in the art would readily recognize the types of molecules that are encompassed by the phrase "trimerising domain that is derived from tetranectin." Applicants, therefore, contend that the trimeric polypeptides of claim 1 have been adequately described.

Applicants respectfully disagree with the Action's assertion that the specification does not provide an adequate written description of the trimeric polypeptides of claims 18 and 19. As discussed above, those of ordinary skill in the art, reading the '906 publication, would readily understand the types of structural changes that could be made to the TTSE sequence in order to generate a trimeric polypeptide having a trimerising domain comprising a sequence having at least 68% (claim 18) or 92% (claim 19) amino acid sequence identity with the sequence of SEQ ID NO: 81.

In view of the specification's express teachings and knowledge in the art at the time of filing of the instant application (*see, e.g.*, the '906 publication), Applicants contend that the trimeric polypeptides of the instant invention have been described in sufficient detail such that one of ordinary skill in the art would conclude that Applicants had possession of the claimed invention. Applicants therefore contend that claims claims 1, 18-23, 30, and 35 satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, and respectfully request that this ground of rejection be withdrawn.

b. Rejection of claims 1, 18-23, 30, and 35 under the enablement requirement of 35 U.S.C. § 112, first paragraph

The Office Action asserts a rejection of claims 1, 18-23, 30, and 35 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention. The Action states that the specification, while being enabling for a trimeric polypeptide comprising three monomers, wherein each monomer comprises the amino acid sequence of SEQ ID NOs: 106, 107, or 108, and each monomer further comprises a specific cytokine binding domain and a tetranectin trimerising domain comprising the amino acid sequence of SEQ ID NO: 81, does not reasonably provide enablement for the genus of trimeric polypeptides recited in claims 1, 18, and 19. The Action also states that claim 18 is overly broad in its limitation of "at least 87% identity" because the specification provides no guidance as to which trimeric

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polypeptides comprising a sequence having at least 68% amino acid sequence identity with the sequence of SEQ ID NO: 81 will retain the characteristics of a trimeric polypeptide comprising the sequence of SEQ ID NO: 81. The Action concludes that given the breadth of the claims, the unpredictability of the art, the number of working examples in the specification, the level of skill in the art, and the guidance provided in the specification and prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Applicants respectfully disagree with the Action's assertion that the specification does not reasonably provide enablement for the genus of trimeric polypeptides recited in claims 1, 18, and 19. As described in section 2(a) above, the specification contains substantial teachings about the portion of the claimed trimeric polypeptide that is a specific binding member capable of binding a trimeric cytokine, and further, states that the trimerising domain that is derived from tetranectin of the claimed trimeric polypeptides comprises a tetranectin trimerising structural element (also called TTSE), which is described in detail in International Publication No. WO 98/56906 (the '906 publication). One of ordinary skill in the art would therefore readily recognize how to make and use the claimed trimeric polypeptides of the instant invention.

Applicants respectfully contend that the rejection based on the enablement requirement of 35 U.S.C. § 112, first paragraph, has been traversed by argument, and request that the Examiner withdraw this ground of rejection.

Applicants respectfully contend that the rejections based on 35 U.S.C. § 112, first paragraph, have been traversed by argument, and request that the Examiner withdraw all rejections made on this basis.

2. Rejection of claim 35 under 35 U.S.C. § 112, second paragraph

The Office Action asserts a rejection of claim 35 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as their invention. The Action states that claim 35 is vague and indefinite for reciting the phrase "mutagenized to" rather than the conventional phrase "substituted with."

Applicants respectfully contend that one of ordinary skill in the art would readily understand that the phrase "the cysteine residue number 50 is mutagenized to serine, threonine, methionine, or

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any other amino acid residue" means that the cysteine residue at position 50 of the recited trimeric polypeptide is changed to (or substituted with) serine, threonine, methionine, or any other amino acid residue. However, in order to expedite prosecution of the pending claims to allowance and more particularly point out and distinctly claim the subject matter that Applicants regard as their invention, and in Applicants' view because it will have no substantive effect on the proper scope of the pending claims, Applicants have amended claim 35 as suggested in the Action to replace the phrase "mutagenized to" with the phrase "substituted with." Applicants respectfully contend that claim 35 satisfies the requirements of 35 U.S.C. § 112, second paragraph, and therefore, request withdrawal of this rejection.

3. Provisional rejection of claims 1, 18-20, and 30 for obviousness-type double patenting

The Action asserts a provisional rejection of claims 1, 18-20, and 30 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 56-68 of U.S. Application No. 11/452,434 (the '434 application). The Action states that while the conflicting claims are not identical, they are not patentably distinct from each other since the claims of the instant application encompass a trimeric polypeptide comprising three monomers, wherein each monomer comprises a cytokine binding member domain and a tetranectin trimerising domain, and thus, encompass subject matter that is a species of the claimed subject matter of the '434 application. The Action also states that that in view of the '434 application, the trimeric polypeptides of the instant application would have been obvious to one of ordinary skill in the art at the time the present invention was made. The Action further states that a trimeric polypeptide found to infringe the claims of the '434 application would also infringe the claims of the instant application.

Applicants acknowledge the provisional rejection under the doctrine of obviousness-type double patenting, and elect to address this ground of rejection upon notification that this rejection has been made non-provisional, all other conditions for patentability have been met, and the instant claims are otherwise in condition for allowance.

CONCLUSIONS

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended. Allowance of the claims is thereby respectfully solicited.

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If Examiner Mertz believes it to be helpful, she is invited to contact the undersigned representative by telephone at 312-913-0001.

Respectfully submitted,
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Dated: December 22, 2008

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EXHIBIT A

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Glu Pro Pro Thr Gln Lys Pro Lys Lys Ile Val Asn Ala Lys Lys Asp
1               5                  10                  15

                                          d   e   f   g   a   b   c
Val Val Asn Thr Lys Met Phe Glu Glu LEU Lys Ser Arg Leu Asp Thr
            20                  25                  30

 d   e   f   g   a   b   c   d   e   f   g   a   b   c   d   e
LEU Ala Gln GLU VAL Ala Leu LEU LYS GLU Gln GLN ALA LEU GLN THR
        35                  40                  45

 f   g   a
VAL CYS LEU Lys Gly Thr Lys Val His Met Lys Cys Phe Leu Ala Phe
    50                  55                  60

Thr Gln Thr Lys Thr Phe His Glu Ala Ser Glu Asp Cys Ile Ser Arg
65                  70                  75                  80

Gly Gly Thr Leu Ser Thr Pro Gln Thr Gly Ser Glu Asn Asp Ala Leu
                85                  90                  95

Tyr Glu Tyr Leu Arg Gln Ser Val Gly Asn Glu Ala Glu Ile Trp Leu
            100                 105                 110

Gly Leu Asn Asp Met Ala Ala Glu Gly Thr Trp Val Asp Met Thr Gly
        115                 120                 125

Ala Arg Ile Ala Tyr Lys Asn Trp Glu Thr Glu Ile Thr Ala Gln Pro
    130                 135                 140

Asp Gly Gly Lys Thr Glu Asn Cys Ala Val Leu Ser Gly Ala Ala Asn
145                 150                 155                 160

Gly Lys Trp Phe Asp Lys Arg Cys Arg Asp Gln Leu Pro Tyr Ile Cys
                165                 170                 175

Gln Phe Gly Ile Val
            180
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